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## **Idiopathic Stevens-Johnson syndrome and toxic epidermal necrolysis: prevalence and patients characteristics**

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***To the Editor:***

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are considered as severe cutaneous adverse reactions (SCARs) to drugs. However, in some cases, no causative drug is identified. Cases of “non-toxic” SJS/TEN cases have been associated to *Mycoplasma pneumoniae* infection or connective tissue diseases, or are considered as idiopathic.<sup>1</sup> Very few data are available about idiopathic cases of SJS/TEN.

Our retrospective study included 193 patients hospitalized in our center (i.e., the French referral center for epidermal necrolysis) for SJS/TEN during the 2005-2016 period. Four were excluded from the analyses (**Figure**). For 2 (1.1%) of the 189 studied patients, *Mycoplasma pneumoniae* infection was identified as the most probable cause of SJS/TEN (**Figure**). The diagnosis of SJS/TEN-like connective tissue was made for 3 (1.6%) other patients (**Figure**). Two of them were diagnosed with lupus erythematosus. For the other, a past history of Sjogren’s syndrome, a progressive cutaneous involvement over a 13 days period, concomitant arthralgias, and positive antinuclear (titer: 1/320) and anti-double-stranded-DNA (titer: 20 IU/mL) made possible the diagnosis of SJS/TEN-like connective tissue disease. Lastly, 12 (6.3%) patients without underlying connective tissue disease or *Mycoplasma pneumoniae* infection were considered as idiopathic SJS/TEN. For these patients, no initiation of systemic drug was found within the month preceding the start of skin and/or mucous symptoms, despite a thorough drug investigation (patient, relatives, general practitioner and/or pharmacy). One of them was 2-month pregnant and another had concomitant streptococcal abscessed tonsillitis. By comparison to patients with drug-induced SJS/TEN, those with idiopathic SJS/TEN were younger and tended to have a less severe skin involvement (**Table**). No biological parameters performed routinely on admission were clearly discriminative.

Few data are available regarding SJS/TEN cases not related to drug exposure. Review articles often report that no causative drug is identified for 20-30% of SJS/TEN<sup>2,3</sup>, even though lower proportions (i.e.,  $\leq 15\%$ ) have been found in cohort studies.<sup>3,4</sup> However, these proportions report both patients with no drug exposure and patients exposed to drugs for whom the causality assessment for each drug is considered as ‘very unlikely’ or ‘unlikely’ using an algorithm for assessment of drug causality.<sup>5</sup>

In a previous study of 379 patients included in the euroSCAR study between 1997 and 2001, 7 patients (1.8%) had not received any systemic drug in the 4 weeks before the onset of the skin/mucous symptoms.<sup>4</sup> More recently, in the United-States, the Society of Dermatology Hospitalists SJS/TEN Study Group found that 8.7% of SJS/TEN (n=405) occurred in patients not exposed to a culprit drug.<sup>3</sup>

In conclusion, even though systematic screening for *Mycoplasma pneumoniae* infection or lupus erythematosus could be considered in all patients with SJS/TEN for whom no culprit drug is identify, these etiologies are unlikely to account for the majority of SJS/TEN not induced by drugs, as suggested by our study. Inadvertent intake of drugs, for instance by consuming meat or milk containing occult veterinary drugs such as non-steroidal anti-inflammatory drugs, has been hypothesized as a possible cause of idiopathic SJS/TEN.<sup>5</sup> However, this hypothesis has not been confirmed so far.<sup>5</sup>

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**Figure legend:** study flow chart

**Table 1:** patients' characteristics

	Idiopathic SJS/TEN N=12	Drug-induced SJS/TEN N=172	P-value
Age (years), median [IQR]	31 [23-43]	47 [35-61]	0.004
Female, n (%)	9 (75.0)	89 (51.7)	0.10
Scorten score at admission, median [IQR]*	0.5 [0-2]	1 [1-2]	0.04
Temperature at admission (°C), median [IQR]	39.1 [37.6-40.1]	38.3 [37.4-39.2]	0.21
Skin detachment (%), median [IQR]			
At admission	6 [2-13]	10 [2-20]	0.39
At day 1	6 [2-12]	13 [4-25]	0.09
At day 5	3 [1-9]	16 [4-35]	0.02
Biological parameters at admission, median [IQR]			
Urea (mmol/l)	3.7 [3.4-4.7]	5.3 [3.5-8.0]	0.05
Creatinine (µmol/l)	57 [49-75]	82 [64-99]	0.008
Glucose (mmol/l)	7.3 [5.7-7.7]	6.1 [5.1-7.9]	0.50
AP (IU/liter)	51 [38-63]	64 [49-85]	0.04
ALT (IU/liter)	35 [22-51]	38 [24-79]	0.30
AST (IU/liter)	36 [27-57]	40 [25-68]	0.50
GGT (IU/liter)	29 [19-46]	52 [26-108]	0.05
LDH (IU/liter)	250 [129-355]	291 [184-415]	0.35
Leucocytes (10 <sup>6</sup> /liter)	5800 [3600-8400]	5850 [4450-7950]	0.59
Hemoglobin (gm/dl)	11.7 [10.5-12.4]	11.9 [10.7-13.1]	0.82
Platelets (10 <sup>9</sup> /liter)	184 [131-253]	210 [168-291]	0.25
ICU admission, n (%)	4 (33.3)	54 (31.4)	1.0
In-hospital mortality, n (%)	0 (0)	17 (9.9)	0.61

IQR: interquartile range; ALT : alanine transaminase; AST : aspartate transaminase; AP: alkaline phosphatase; GGT: gamma glutamyl transferase; ICU, intensive care unit

Scorten: severity-of-illness score for toxic epidermal necrolysis (according to the study by Bastuji-garin et al, J Invest Dermatol. 2000;115:149-5)

The Fischer's exact test and the Wilcoxon rank-sum test were used to compare categorical and quantitative data, respectively.

**Figure:** study flow chart

